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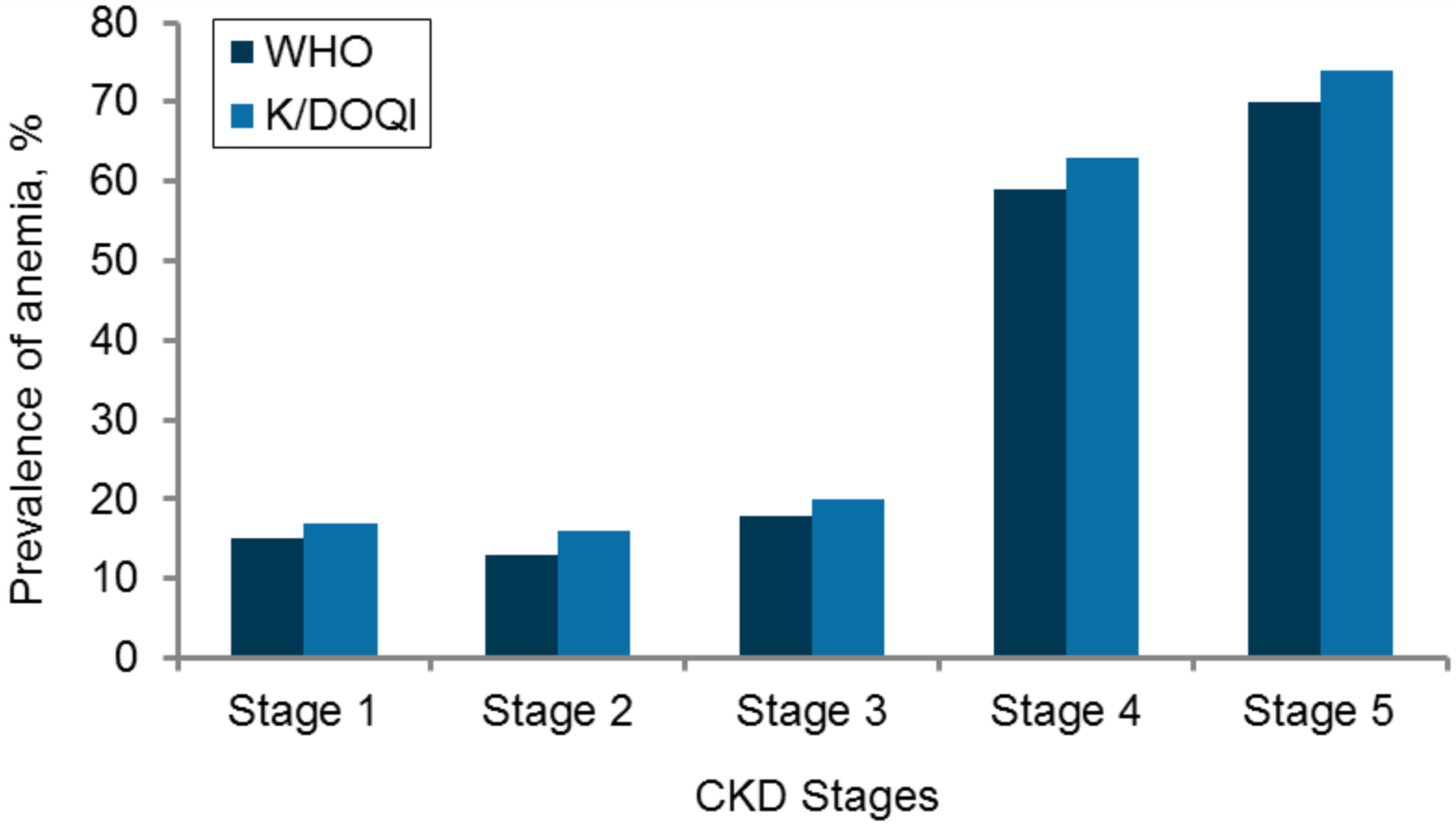
Anemia Prevalence and CKD Stage



K/DOQI = kidney disease outcomes quality initiative

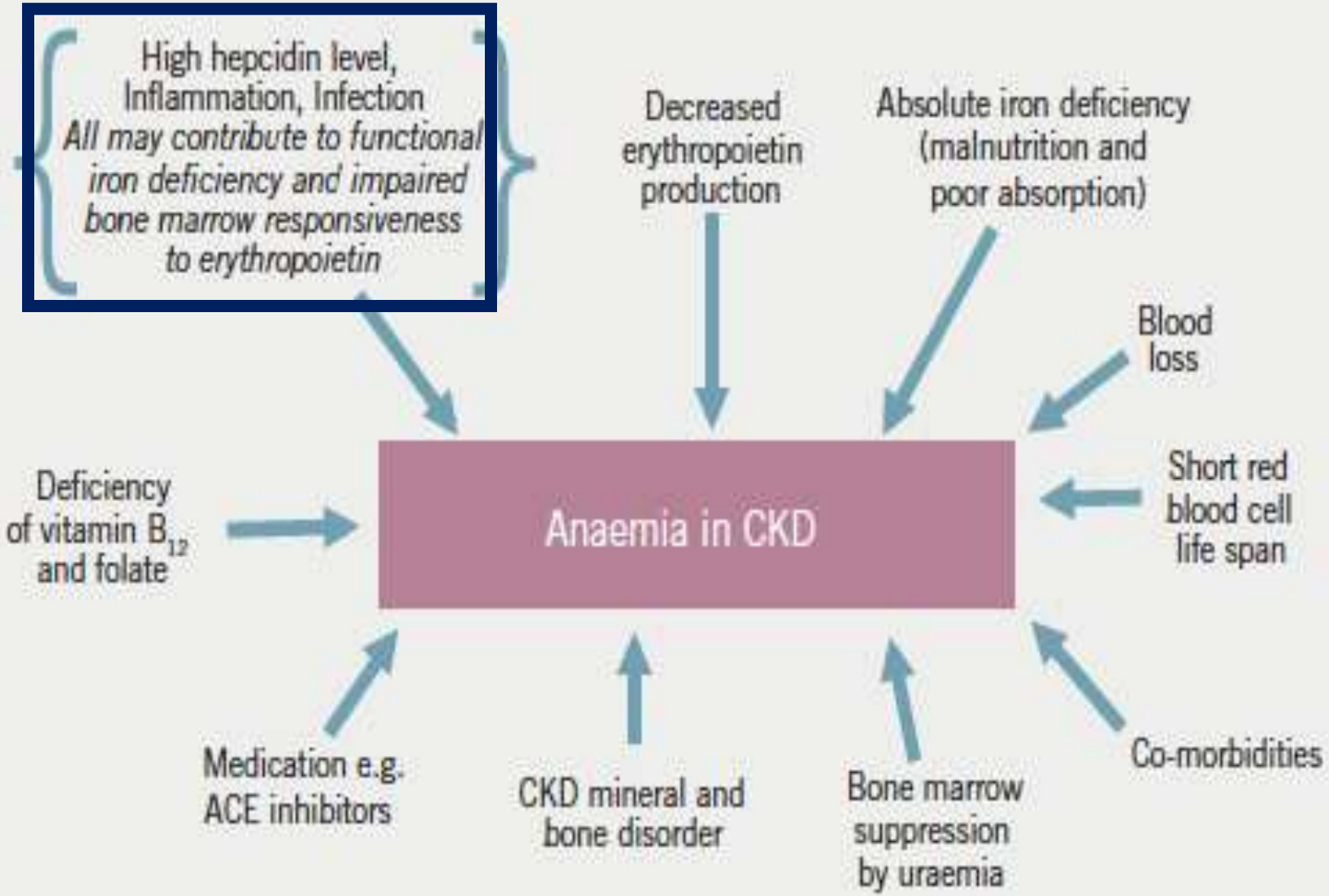
Republished from McFarlane SI, Chen SC, Whaley-Connell AT, et al. Prevalence and associations of anemia of CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. *Am J Kidney Dis*. 2008;51:S46-S55, with permission from Elsevier.

Hemoglobin Levels in Patients Undergoing Dialysis

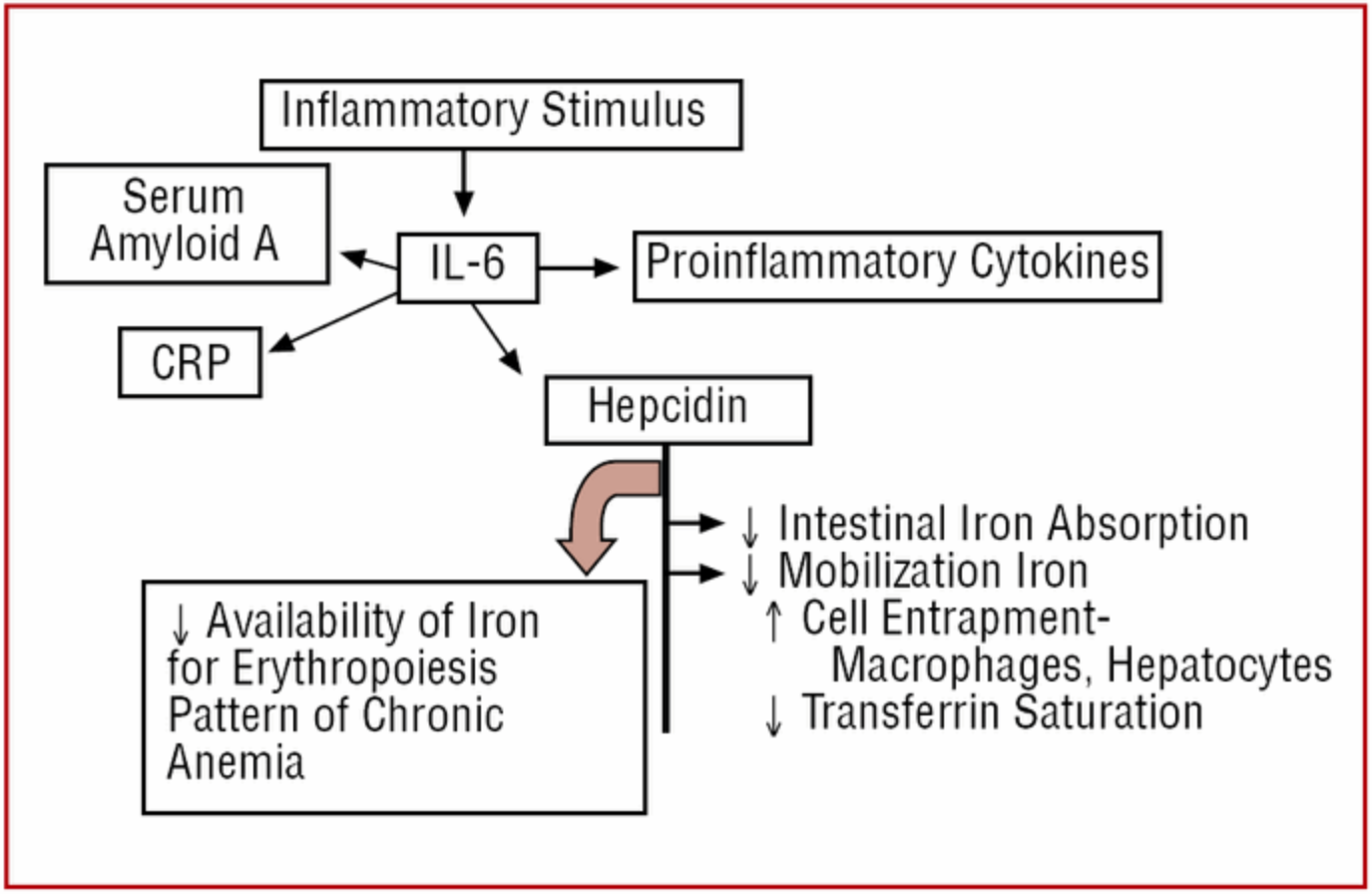
About 50% of patients starting dialysis have hemoglobin < 10 g/dL

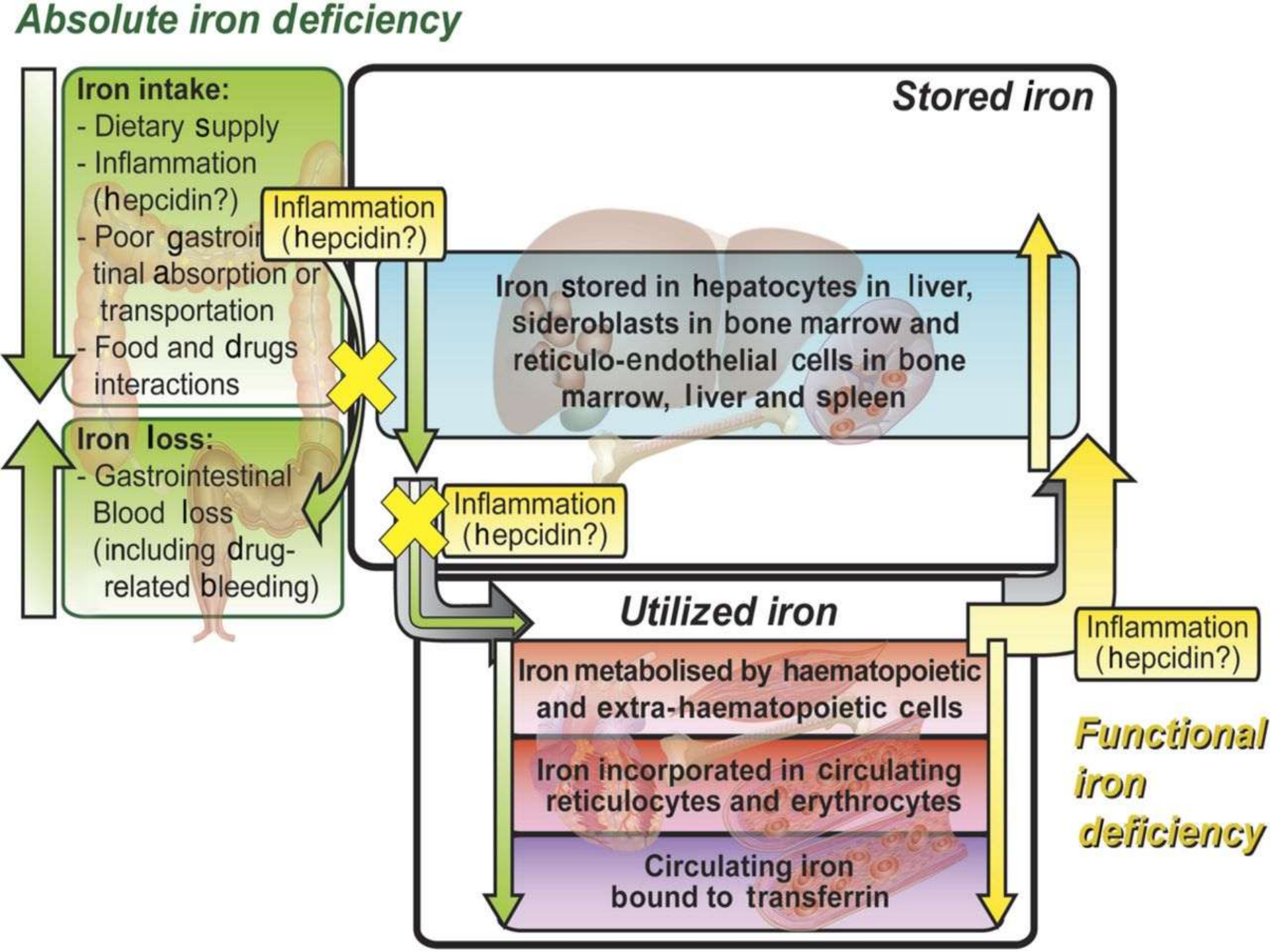
	Serum albumin	Hemoglobin < 10 g/dL
Age		
20-44	56.6	57.0
45-64	58.1	54.0
65-74	56.3	51.8
75+	57.9	48.2
Gender		
Male	56.2	50.8
Female	58.6	54.5
Race		
White	56.5	49.5
African American	59.6	59.9
Native American	68.2	55.0
Asian	51.3	47.3
Hispanic	60.6	55.3
Primary diagnosis		
Diabetes	61.8	53.7
Hypertension	52.8	51.3
Glomerulonephritis	51.7	49.3
Cystic kidney disease	23.2	31.4
All	57.2	52.4

U.S. Renal Data System, USRDS 2011 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2011.



Adapted from Agarwal AK. *J A Med Dir Assoc* 2006;**7**:S7–S12


Inflammatory Stimulus
Serum Amyloid A
IL-6
Proinflammatory Cytokines
CRP
Hepcidin
↓ Intestinal Iron Absorption
↓ Mobilization Iron
↑ Cell Entrapment-
Macrophages, Hepatocytes
↓ Transferrin Saturation
↓ Availability of Iron for Erythropoiesis Pattern of Chronic Anemia


Absolute iron deficiency
Iron intake:
- Dietary supply
- Inflammation (hepcidin?)
- Poor gastrointestinal absorption or transportation
- Food and drugs interactions
Iron loss:
- Gastrointestinal Blood loss (including drug-related bleeding)
Inflammation (hepcidin?)
Stored iron
Iron stored in hepatocytes in liver, sideroblasts in bone marrow and reticulo-endothelial cells in bone marrow, liver and spleen
Inflammation (hepcidin?)
Utilized iron
Iron metabolised by haematopoietic and extra-haematopoietic cells
Iron incorporated in circulating reticulocytes and erythrocytes
Circulating iron bound to transferrin
Inflammation (hepcidin?)
Functional iron deficiency

Iron deficiency in CKD
with ESA therapy

↑ **iron need**

Erythropoietin is a hormone secreting by the kidney to increase the red blood cells production by the bone marrow.

Diagnosis of anemia in CKD

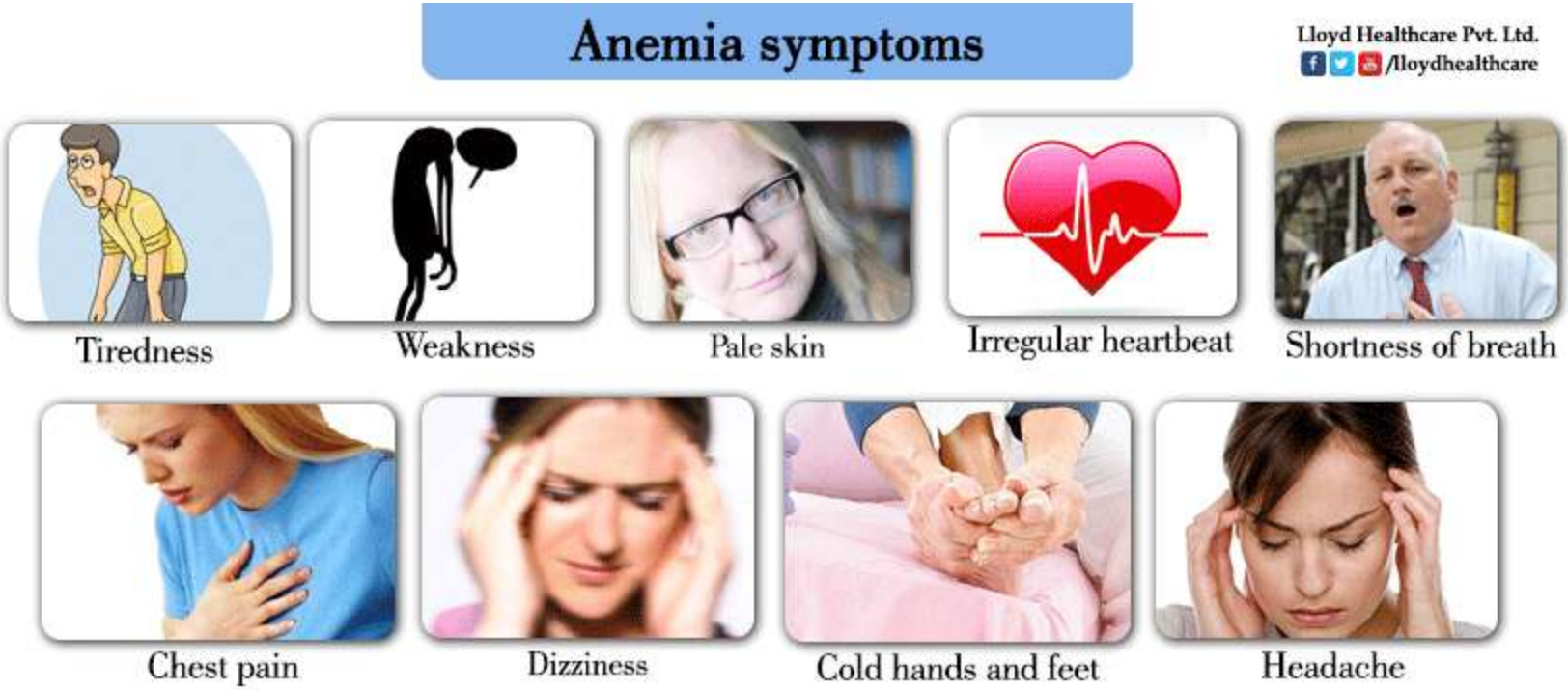
- **When to investigate?**
- **What are levels of HB needed to define anemia in CKD?**
- **What are markers of iron deficiency to be considered?**

When to investigate?

eGFR ≤60 ml/min/1.73m2

should trigger investigation of anaemia inCKD

Frequency of testing for anemia



Frequency of testing for anemia

1.1.1: For CKD patients without anemia measure Hb concentration when

clinically indicated

&

CKD 3	CKD 4–5ND	CKD 5HD and CKD 5PD
at least annually	twice per year	at least every 3 months

Frequency of testing for anemia

- **1.1.2: For CKD patients with anemia not being treated with an ESA, measure Hb concentration when**

clinically indicated

&

CKD 3–5ND and CKD 5PD	CKD 5HD
at least every 3 months	at least monthly

What are levels of HB needed to define anemia in CKD?

Age or gender group	Hb below (g/dl)
Children	
6 months to 5 years	11.0
5 to 11 years	11.5
12 to 14 years	12.0
Women > 15 years (non-pregnant)	**12.0**
Men > 15 years	**13.0**

Preliminary investigations:

1.3: In patients with CKD and anemia (regardless of age and CKD stage)

- ❑ Complete blood count (CBC), red cell indices, white blood cell count, and differential, and platelet count
- ❑ Absolute reticulocyte count
- ❑ Serum ferritin level
- ❑ Serum transferrin saturation (TSAT)
- ❑ Serum vitamin B12 and folate levels

markers of Iron status

Presence or Absence of Storage iron	Serum Ferritin
Availability of iron to support ongoing erythropoiesis	TSAT ; (serum Iron x 100)/TIBC

Reticulocyte hemoglobin content (CHr), pg	Directly determines iron available for Hb synthesis by measuring Hb in reticulocytes	▪ Indicates immediate availability of iron for Hb synthesis ▪ Early indicator of iron deficiency in ESA treatment
Percentage hypochromic red blood cells (PHRC), %	Measures concentration (%) of hypochromic RBCs	Assay must be performed promptly after sampling to minimize effects of storage on RBCs
Bone marrow iron biopsy, grading index or % erythroblasts with visible iron 	Gold standard for iron status	▪ Invasive procedure is painful, limits clinical application ▪ Grading method is subjective ▪ Inter- and intraobserver variability occurs in evaluating samples
Soluble transferrin receptor (sTfR), µg/mL	Measures transferrin receptors on erythroblasts as a correlate of transferrin expression. As iron deficiency ↑ there is a corresponding ↑ in sTfR on erythroblasts. During ESA treatment, total erythroblast mass ↑, raising sTfR.	▪ Clinician must determine if sTfR increase is due to iron deficiency or response to ESA ▪ Early marker of iron deficiency
Zinc protoporphyrin (ZnPP), µmol/mol	Determines iron status in erythrocytes by measuring incorporation of Zn into protoporphyrin in place of iron	▪ Reflects iron status during Hb synthesis ▪ Allows detection of iron deficiency before onset of anemia
Hepcidin	Hepcidin inhibits iron mobilization from RES and GI absorption as ferritin ↑; hepcidin assay detects functional iron deficiency	No reliable assay currently exists

- **Use percentage of hypochromic red blood cells (% HRC; more than6%), but only if processing of blood sample is possible within 6 hours.**

- **If using % HRC is not possible, use reticulocyte (Hb)content (CHr; less than 29 pg).**

- **If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of :**

✓ **TSAT <20%**

✓ **serum ferritin < 100micrograms/litre**

NICE accredited

www.nice.org.uk/accreditation

June 2015

Do not request TSAT or SF measurement alone to assess iron deficiency status in people with anaemia of CKD.

June 2015

NICE accredited

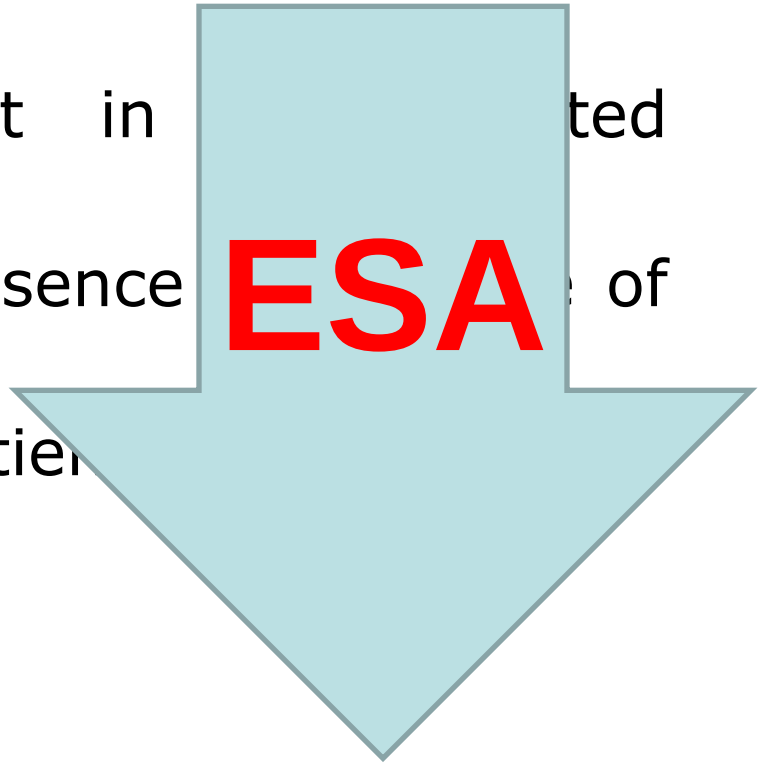
www.nice.org.uk/accreditation

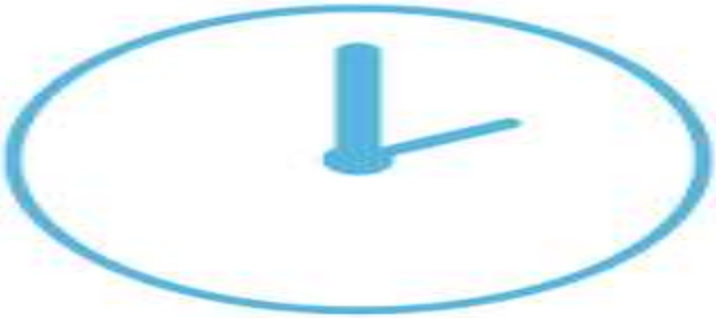
IRON THERAPY IN CKD

Use of iron to treat anemia in CKD

Iron supplementation is widely used in CKD patients:

- To treat iron deficiency
- Prevent its development in ted patients
- Raise Hb levels in the presence of ESA treatment
- Reduce ESA doses in patie treatment.





when to start

Guideline 2.1.2

- For adult CKD patients with anemia **not on iron or ESA therapy**
- a trial of i.v. iron (or in CKD ND patients alternatively a 1–3-month trial of oral iron therapy) if (2C):
  - an increase in Hb concentration without starting ESA treatment is desired and
  - TSAT is ≤30% and ferritin is ≤500 ng/ml .

Guideline 2.1.3

- For adult CKD **patients on ESA therapy who are not receiving iron supplementation**
- a trial of IV iron(or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):
  - an increase in Hb concentration** or a decrease in ESA dose is desired*** and
  - TSAT is ≤ 30% and ferritin is ≤ 500 ng/ml


FERRITIN≤500 ng/ml
TSAT≤ 30%
START
KIDNEY DISEASE
IMPROVING GLOBAL OUTCOMES
KDIGO

Offer iron therapy to people receiving ESA maintenance therapy to keep their:

- **Percentage of hypochromic red blood cells less than 6%**
- **Reticulocyte Hb count or equivalent tests above 29 pg**
- **TSATlevel above 20% and SF level above 100 micrograms/litre**

(unless SF is greater than 800 micrograms/litre)

June 2015

Iron Therapy

Oral Iron Therapy

- Although inexpensive and convenient,
- oral iron therapy has several important limitations

Limitations of oral iron therapies[1,2]

Impaired intestinal iron absorption	• Concomitant food or medication (e.g. phosphate binders, H_2 blockers, proton pump inhibitors) – by raising the pH non-haem foods cannot be absorbed • Exacerbated by elevated hepcidin and other inflammatory cytokine levels in conditions where there is an inflammatory component
May be inadequate during ESA therapy	• Accelerated erythropoiesis can increase demand for iron beyond the amount supplied orally
Gastrointestinal adverse events	• Can affect over 50% of patients • Can adversely affect nutritional intake • Improved if iron tablets are taken with food, but this decreases absorption
Compliance	• Pill burden: usually 2 or 3 tablets per day • Affected by gastrointestinal intolerance
Oxidative stress	• High oral iron doses can saturate the iron transport system if the iron is rapidly released, resulting in oxidative stress

1. Macdougall IC. *Curr Med Res Opin* 2010;26:473–83;
2. Crichton RR *et al. Iron Therapy With a Special Emphasis on Intravenous Administration* (4th edition). UNI-MED Verlag AG, Bremen, Germany, 2008

Table 2. Oral Iron Preparations

Preparation	Pills Required to Provide 200 mg iron, *n*	Tablet Size, mg	Amount of Elemental Iron, (mg)/pill
Ferrous sulfate	3	325	65
Ferrous gluconate	6	325	35
Ferrous fumarate	2	325	108
Iron polysaccharide	2	150	150

Adapted with permission from the National Kidney Foundation.

Oral liposomal iron

- a promising new strategy of oral iron
- high gastrointestinal absorption and bioavailability and a low incidence of side effects

Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial

oral liposomal iron is a safe and efficacious alternative to IV iron gluconate to correct anaemia in ND-CKD patients, although its effects on repletion of iron stores and on stability of Hb after drug discontinuation are lower.

Nephrol Dial Transplant. 2015 Apr;30(4):645-52

Oral Iron Therapy

If the goals of iron supplementation are not met with **a 1–3 month course** of oral iron, it is appropriate to consider IV iron supplementation

IV Iron Therapy

	Iron sucrose	Na Ferric Gluconate	Ferumoxytol	Ferric carboxymaltose	Iron Dextran
FDA approval	**2000**	**1999**	**2009**	**2013**	**1997**
FDA Indications	**IDA in CKD**	**IDA in HD**	**IDA in CKD**	**IDA in CKD**	**IDA when oral iron?**
Availability	100 mg/5 ml	62.5 mg/5 ml ampule or vial	510 mg/17 ml vial	750 mg/15 ml vial	100 mg/2 ml vial
Repletion Dosing	HD: 100 mg per dialysis session CKD-ND: 200mg*5 over 14 days	1000mg (125mg*8 sessions).	510mg*2 (1 week apart).	750 mg ,2nd inj 7 days later	Dose (ml) = 0.0442 (desired Hgb – observed Hgb) x LBW + (0.26 x LBW)

Table 3. Intravenous Iron Preparations

Preparation	Maximum Single Dose	Recommended Dose
Iron dextran	1000 mg	100 mg × 10 doses
Iron gluconate	125 mg	125 mg × 8 doses
Iron sucrose	100 mg	100 mg × 10 doses
Ferumoxytol	510 mg	510 mg × 2 doses

Adapted with permission from the National Kidney Foundation.

Adverse effects of iron therapy

- Allergic reaction.
- Hypotension.
- Dizziness.
- Dyspnea.
- Headache.
- Low back pain.
- Arthralgia.
- Syncope.
- Arthritis.

Some side effects can be reduced by decreasing the dose or rate of infusion.

Sodium ferric gluconate or iron sucrose has better safety profile than iron dextran.

Adverse effects of iron therapy

- High ferritin levels in some studies have been associated with higher **death rates**, but whether elevation of ferritin levels is a marker of excessive iron administration rather than a nonspecific acute phase reactant is not clear.

- At increasingly higher ferritin levels, there is some evidence to indicate that **hepatic deposition** of iron increases

Treatment of Iron Deficiency Anemia

Treatment	Potential Benefits	Potential Risks
IV iron[a]	• Improve hemoglobin levels • Reduce dosing requirements for ESAs	• Accumulation in tissue • Transient increase in oxidative stress (?) • Risk for infection (?) • Increase in plasma non-transferrin-bound iron

what is the optimal route of iron administration?

2.1.4

For CKD ND select the route of iron administration on the basis of:

- the severity of iron deficiency
- availability of venous access,
- response to prior oral iron therapy
- side effects with prior oral or i.v. iron therapy
- patient compliance, and cost

Oral vs IV iron

Not on HD

On HD

Try oral iron

IV iron is mandatory

Iron status evaluation

Monitoring treatment of anemia of CKD

Monitoring iron status

1 week after receiving intravenous iron.

ESAs: monitoring iron status during treatment

The marker of iron status should be monitored every 1–3 months in people receiving hemodialysis.

In people who are pre-dialysis or receiving peritoneal dialysis, levels are typically monitored every 3 months.

NICE 2015

2.2.1

- Evaluate iron status (TSAT and ferritin) at least **every 3 months** during ESA therapy, including the decision to start or continue iron therapy. (Not Graded).

2.2.2

Test iron status (TSAT and ferritin) more frequently when

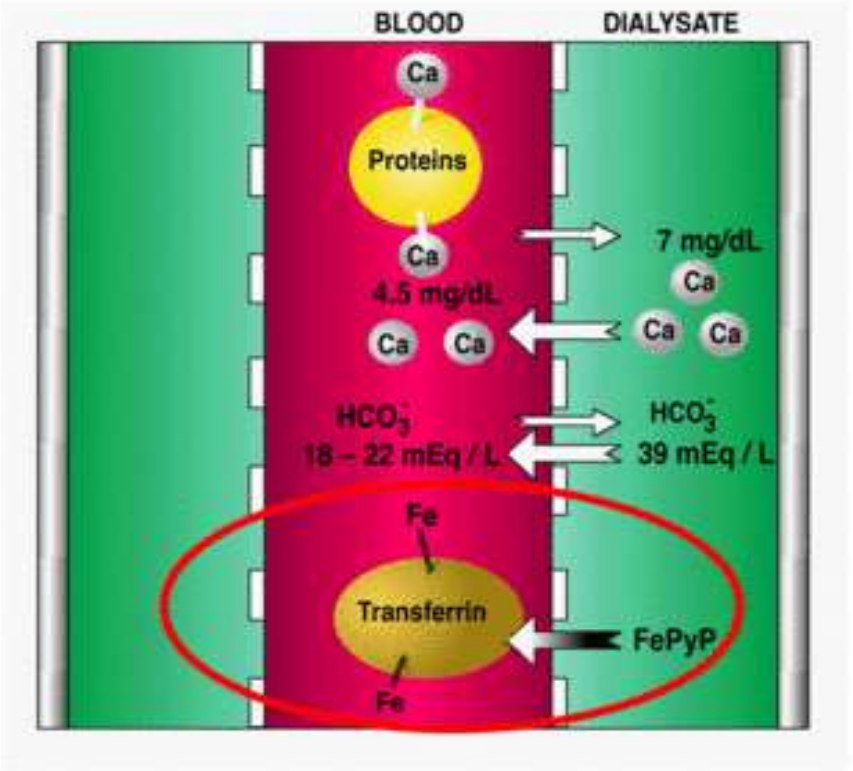
- initiating or increasing ESA dose
- there is blood loss
- monitoring response after a course of IV iron
- circumstances where iron stores may become depleted. (Not Graded)

What is new?

SFP Iron Delivered via Dialysate

- Iron-citrate-pyrophosphate complex: soluble, non-colloidal salt that is not conjugated with a sugar moiety.
- SFP is infused into the blood via dialysate over the course of the dialysis treatment
- SFP crosses the dialyzer membrane just like calcium and bicarbonate, entering the blood
- **SFP iron simply replaces the 5-7mg of iron that is lost during the dialysis treatment**
- SFP is the only iron in the world that can be delivered via dialysate

Inside Dialyzer Filter



Phosphate Binders

Calcium-based

- Calcium carbonate
- Calcium acetate

Non-calcium-based

- Sevelamer
- Lanthanum carbonate

Newer iron-based binders

- Sucroferric oxyhydroxide (PA21)
- Ferric citrate

FDA Approved: Auryxia™ (ferric citrate)

- Approved on September 5, 2014, by the U.S. Food and Drug Administration (FDA)
  - Auryxia™ (ferric citrate) is an absorbed, iron-based phosphate binder
- INDICATION: For the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on dialysis
- U.S. launch of Auryxia™ at YE
  - Ferric Citrate is currently being marketed in Japan, under the trade name Riona®, by the Company's Japanese partner, Japan Tobacco Inc. and Torii Pharmaceutical Co. Ltd.
- Additional potential growth areas for Ferric Citrate
  - Label expansion: Iron deficiency anemia in non-dialysis dependent chronic kidney disease
  - Geographical expansion: EU and emerging markets

KERYX

PA21

- Chewable iron-based phosphate binder
- Mean decrease of ≈2.0 mg/dL in phosphorus levels in first 12 weeks of treatment
  - Noninferior to sevelamer
- Lower pill burden vs sevelamer: 8 tablets vs 3 tablets
- Minimal absorption of iron (0.02%)
- Common adverse events: gastrointestinal related (diarrhea, discolored stools)

Floege J, et al. *Kidney International*. 2014;86:638-647.[12]

рахмат
danke
謝謝
ngiyabonga
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
welalin
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감사합니다
xièxie
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Hepcidin in Chronic Kidney Disease

Hepcidin: small peptide produced primarily by hepatocytes

- Important regulator of iron homeostasis
  - Limits intestinal iron absorption
  - Regulates iron distribution from body stores, including macrophages
  - Initiates degradation of ferroportin (iron export protein) → inhibition of iron transfer from hepatocytes, duodenal enterocytes, and macrophages into plasma

Chronic kidney disease is associated with a proinflammatory state

- Hepcidin levels are elevated in patients with CKD
  - Contribute to development and severity of CKD-related anemia in patients
- Inflammatory markers can increase hepcidin synthesis → decrease in iron availability for erythropoiesis

Sun CC, et al. *Am J Hematol*. 2012;87:392-400.[2]

Assessment of IV Iron in Patients With Non-Dialysis-Dependent CKD

- 56-week open-label trial of ferric carboxymaltose (FCM) vs oral iron in patients with non-dialysis-dependent CKD
- Patients in study were randomized to 3 groups:
  - FCM: high ferritin (ferritin target 400 to 600 µg/L)
  - FCM: low ferritin (ferritin target 100 to 200 µg/L)
  - Oral iron, ferrous sulfate: 200 mg iron/day
- Conclusion: Intravenous FCM treatment to achieve a higher serum ferritin target (400 to 600 µg/L) reduced initiation of other anemia treatments and improved hemoglobin levels in patients
  - Time to initiation of other anemia treatment: significantly higher vs oral iron group (P=.026)
  - More patients achieved increase in hemoglobin (≥1 g/dL) vs oral iron group and low-ferritin FCM group (P < .001)

Macdougall IC, et al. *Nephrol Dial Transplant*. 2014;29:2075-2084.[8]

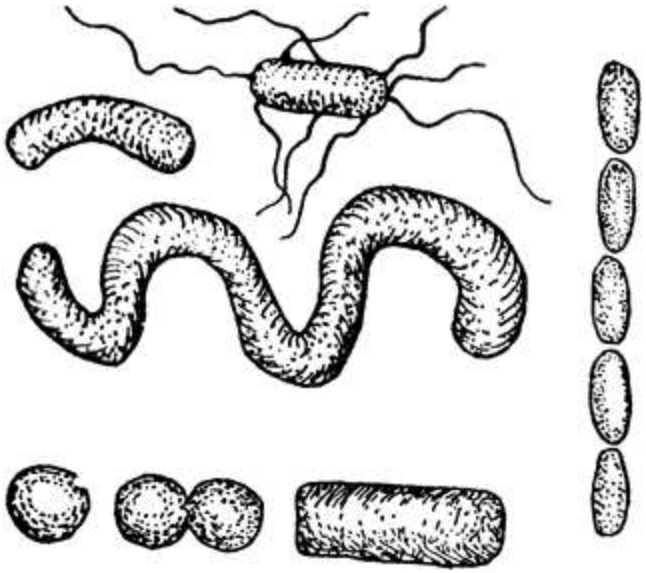
DOPPS Study

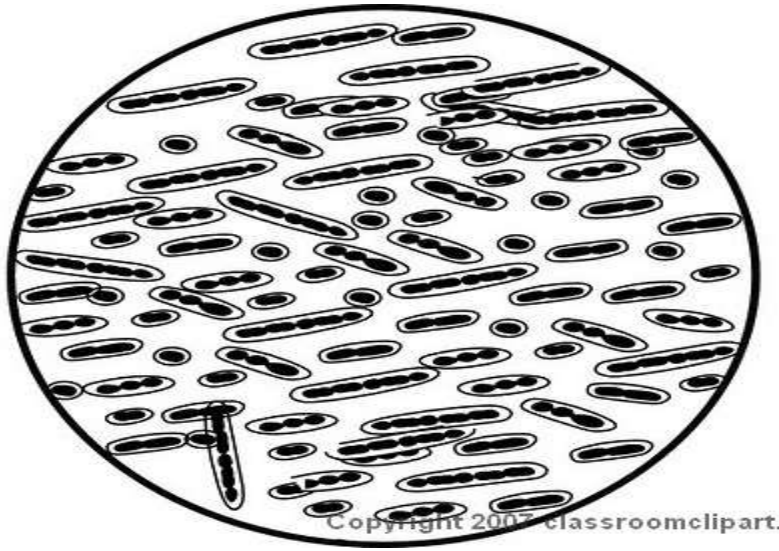
- Analyzed the association of IV iron use with mortality in 32,435 patients internationally
- IV iron use was assessed over 4 months; follow-up time was 1.7 years
- Findings:
  - 18% increased risk for mortality with doses of 400 mg/mo or more vs 100 to 199 mg/mo
  - 12% increased risk for mortality with doses of 300 mg/mo or more vs less than 300 mg/mo
  - 12% increased risk for hospitalizations with doses of 300 mg/mo or more
  - For monthly iron doses normalized to body weight, there was an increased risk (35%) for cardiovascular-related mortality at ≥6 mg/kg/mo vs 1 to 2 mg/kg/mo
  - Residual confounding limits findings in this observational study

Bailie GR, et al. *Kidney Int*. 2015;87:162-168.[9]

Can Iron Worsen Infection?

- Iron serves as an essential nutrient for metabolic pathways in both humans and microorganisms. Pathogenic microorganisms, including bacteria, fungi, and protozoa, require iron for growth and proliferation.





Testing should be delayed 1 week after IV Iro

IRON STATUS EVALUATION

- 2.2.1: Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (Not Graded).

- 2.2.2: Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (Not Graded)